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Signed this 17th day of December 2007

C. E. SITCH
Managing Director - UK Translation Division
For and on behalf of RWS Group Ltd

FEDERAL REPUBLIC OF GERMANY

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Schäfer

Novel combination of glucocorticoids and phosphodiesterase-4 inhibitors for treating respiratory diseases, allergic diseases, asthma and chronic obstructive pulmonary diseases

The present invention relates to a novel combination of a glucocorticoid, especially loteprednol, and at least one phosphodiesterase-4 inhibitor, especially the hydroxyindole derivative N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide, for a simultaneous, sequential or separate administration in the treatment of respiratory diseases, allergic diseases, asthma and chronic obstructive pulmonary diseases.

Allergic diseases and chronic obstructive pulmonary diseases (COPD) are based on inflammatory processes characterized by an increased number of inflammatory cells and increased release or secretion of inflammation mediators. Studies over the last 20 years have revealed that inflammation of the respiratory tract is of central importance for the respiratory dysfunction in asthma and COPD. Comparable changes have been observed in allergic inflammations of the nose and of the eyes. Normally, the mucosa is infiltrated by a large number of cells, including mast cells, eosinophils and lymphocytes. These cells release a number of mediators, including in particular interleukin-4 (IL-4), GM-CSF (granulocyte/macrophage colony-stimulating factor) and the tumor necrosis factor α (TNF-α), which eventually bring about the inflammations and the symptoms of allergic diseases and of COPD.

At the present time, a similar anti-inflammatory therapeutic approach is followed for all allergic diseases. The pathology of these diseases has revealed

that the inflammatory process in the mucosa of patients primarily determines the symptom activity. Of the anti-inflammatory compounds currently available for the treatment of asthma, rhinitis or conjunctivitis, glucocorticoids are the most effective. Active ingredients which can be administered topically by inhalational, intranasal or intraocular administration are preferably employed. On the basis of the successful use of inhalable glucocorticoids in the treatment and prevention of respiratory inflammations and permanent lung damage in asthma patients, this therapeutic approach has also been applied to COPD patients although there are no data which might unambiguously prove a long-term efficacy of these active ingredients in COPD patients (Whittaker AJ, Spiro SG; Curr Opin Pum Med 2000; 6:104-9).

One of the most important anti-inflammatory properties of glucocorticoids arises from inhibition of cytokine release. It is known that several cytokines such as IL-4, IL-5, GM-CSF and TNF-α are involved in respiratory inflammation. The efficacy of glucocorticoids can in part be explained by the inhibitory effect on cytokine synthesis and cytokine release (Marx et al.; Pulm Pharmacol Ther 2002; 15:7-15).

One disadvantage of glucocorticoids arises from their possible systemic side effects such as, for example, growth retardation or else osteoporosis. Sensible measures for reducing the risk of side effects on topical administration of glucocorticoids include the use of the minimum effective dose or restriction of the systemic availability of the active ingredient. A novel route is opened up by the use of so-called soft steroids. In contrast to other glucocorticoids, most of which undergo degradation to pharmacodynamically inactive metabolites only in the liver, the soft

steroids undergo partial metabolic inactivation even at the site of their administration (intranasal, ocular or intrapulmonary). Following this partial local metabolism, only very little, or no, pharmacodynamically active substance reaches the systemic blood circulation, so that the steroid-specific side effects are not to be expected in practice. The most prominent example of this novel class of active ingredients is loteprednol, which is already approved for the therapy of allergic conjunctivitis and uveitis.

A further class of potential therapeutics for allergic diseases and COPD comprises the phosphodiesterase-4 inhibitors. Phosphodiesterase enzymes are responsible for the inactivation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Inhibition of phosphodiesterase-4 leads to an increase in cAMP in the cells, in turn leading to downregulation of the function of virtually all proinflammatory cells or immune cells. It is of interest that inflammatory cells involved in the pathogenesis of diseases such as asthma, conjunctivitis, rhinitis or chronic obstructive pulmonary disease preferentially express the phosphodiesterase-4 enzymes.

In recent years there have been advances in the development of phosphodiesterase-4 inhibitors which can be employed for the therapy of allergic diseases, asthma or COPD. It has been possible to show the in vitro inhibitory activity on cytokine release and the therapeutic efficacy in asthma models for example for the active ingredients roflumilast, cilomilast or else piclamilast (Torphy et al.; Pulm Pharmacol Ther 1999; 12:131-5; Poppe et al.; Allergy 2000; 55(Suppl 63):270; Giembycz MA; Expert Opin Investig Drugs 2001; 10:1361-79; Ezeamuzie CI; Eur J Pharmacol 2001; 417:11-8).

There is particular interest in a novel class of substituted hydroxyindoles which are described in DE 19 818 964, DE 19 917 504 and US 6,251,923, and also novel 7-azaindoles which are disclosed in DE 10 053 275 and PCT/EP 01/12376.

It has now surprisingly been found that the novel combination of a glucocorticoid with at least one phosphodiesterase-4 inhibitor is advantageous in the treatment of respiratory diseases, allergic diseases, asthma and/or chronic obstructive pulmonary diseases. Add-on therapy of a phosphodiesterase-4 inhibitor, especially the hydroxyindole derivative N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxy-indol-3-yl]-2-oxoacetamide, which is administered orally, intranasally or by inhalation, with topical glucocorticoids, especially loteprednol, is distinguished by improved therapeutic efficacy as well as by the occurrence of few side effects.

The invention serves to improve the therapy of respiratory diseases, allergic diseases, asthma and chronic obstructive pulmonary diseases, as well as the prophylaxis thereof. It is possible with a phosphodiesterase-4 inhibitor present in the combination and with a glucocorticoid successfully to control the inflammations which underlie the pathological states. Moreover, add-on therapy with phosphodiesterase-4 inhibitor leads to a smaller use of glucocorticoids, thus reducing the risk of side effects.

The present invention therefore relates to a composition which comprises a glucocorticoid and at least one phosphodiesterase-4 inhibitor in fixed or free combination, and to the use thereof for producing a medicament. The invention also relates to a

medicament for the treatment of respiratory diseases, allergic diseases, asthma and/or chronic obstructive pulmonary diseases, which comprises as active ingredient a glucocorticoid and at least one phosphodiesterase-4 inhibitor in fixed or free combination, and to a process for the production thereof.

Glucocorticoids which can be employed for the purposes of the present invention are all glucocorticoids known to the skilled worker. So-called soft steroids are preferably used. The examples which may be cited of glucocorticoids which can be employed according to the invention are beclomethasone (9-chloro-11β,17,21-trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione), especially beclomethasone dipropionate, budesonide (16α,17-butylidenedioxy-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione), ciclesonide (see, for example, WO 98/52542 and literature cited therein), fluticasone (S-(fluoromethyl) 6α,9-difluoro-11β-carbothioate), especially fluticasone propionate, mometasone (9,21-dichloro-11β,17-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione), in particular mometasone fuorate, and loteprednol, especially loteprednol etabonate (chloromethyl 17□-[(ethoxycarbonyl)oxy]-11□-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate).

In a preferred embodiment of the invention, loteprednol and its pharmaceutically acceptable esters, especially loteprednol etabonate, is used as soft steroid. The preparation of loteprednol and loteprednol etabonate is described for example in the German patent DE 3 126 732, the corresponding US patent 4,996,335 and the corresponding Japanese patent JP-89011037.

Further soft steroids suitable according to the invention are described for example in the German

patent DE 3 786 174, the corresponding patent EP 0 334 853 and the corresponding US patent 4,710,495.

Phosphodiesterase-4 inhibitors which can be employed for the purposes of the present invention are all phosphodiesterase-4 inhibitors known to the skilled worker. These include the class of substituted hydroxyindole derivatives which are described in DE 19 818 964, DE 19 917 504 and US 6,251,923, and also novel 7-azaindole derivatives which are disclosed in DE 10 053 275 and PCT/EP 01/12376. Examples of phosphodiesterase-4 inhibitors which can be used according to the invention are rolipram ((R)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone), roflumilast (Byk-Gulden), piclamilast (Rhone-Poulenc Rorer), cilomilast (GlaxoSmithKline) and the hydroxyindole derivative N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxo-acetamide). Particular preference is given to the substituted hydroxyindole derivative N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxy-indol-3-yl]-2-oxoacetamide, which is described for example in DE 19 818 964. The phosphodiesterase-4 inhibitors can also be employed as pharmaceutically acceptable salts as are known to the skilled worker.

In a preferred embodiment, a combination of the active ingredients loteprednol etabonate and N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxy-indol-3-yl]-2-oxoacetamide) is used.

It is possible by topical administration of the two active ingredients (steroid and phosphodiesterase-4 inhibitor) to achieve therapeutically effective concentrations even with low dosages. The two active ingredients may in this connection be administered simultaneously, sequentially or separately in free or

fixed combination. They can be administered either in a single dose form or as two separate formulations which may be identical or different. Thus, the two active ingredients can for example be administered separately as two oral formulations, or one active ingredient is in the form of an oral formulation and the other is in topical form (intranasal, inhalational). Addition can take place at the same time, i.e. simultaneously, or at separate times, by which is meant both short and long intervals, such as, for example, administration of loteprednol in the evening and administration of the phosphodiesterase-4 inhibitor in the morning, or else vice versa.

In an advantageous embodiment, the active components of this combination are present in the form of a fixed combination, thus simplifying use for the patient.

The inventive combination of a glucocorticoid, in particular of a soft steroid, with one phosphodiesterase-4 inhibitor can be administered both prophylactically and after appearance of symptoms. They can also be used to retard or prevent progression of the diseases.

In one embodiment of the invention, the phosphodiesterase-4 inhibitor can also be administered orally. Customary pharmaceutical formulations are used in this case, such as tablets, syrup, capsules, preparations with slowed release, pastilles or effervescent granules.

Solid pharmaceutical forms such as tablets may comprise inert ingredients and carriers such as, for example, calcium carbonate, calcium phosphate, sodium phosphate, lactose, starch, mannitol, alginates, gelatin, guar gum, magnesium stearate or aluminum stearate, methyl-

cellulose, talc, colloidal silicas, silicone oil, high molecular weight fatty acids (such as stearic acid), agar-agar or vegetable or animal fats and oils, solid high molecular weight polymers (such as polyethylene glycol); preparations suitable for oral administrations may, where appropriate, comprise additional flavorings or sweeteners. The compositions in capsule form can be produced by generally customary processes, for example by using the aforementioned carriers in a hard gelatin capsule shell. Syrup formulations normally consist of a suspension or solution of the compound or of a salt thereof in a liquid carrier such as, for example, ethanol, peanut oil, olive oil, glycerol or water, it being possible for flavorings and colorants to be present. For compositions in the form of soft gelatin capsules it is possible to employ pharmaceutical carriers normally used for producing dispersions or suspensions, such as, for example, aqueous gums, celluloses, silicates or oils, which are incorporated into a soft gelatin capsule shell.

Topical formulations, which include in particular intranasal and inhalational formulations, are preferred for the purposes of the present invention. Intranasal preparations may be in the form of aqueous or oily solutions, suspensions or emulsions which can be administered by the intranasal route. For the administration of an active ingredient by inhalation, it can be administered in the form of a suspension, solution or emulsion which is administered as dry powder or as aerosol, it being possible to use customary propellants such as fluorinated hydrocarbons such as, for example, trichlorofluoromethane.

The preferred soft steroid loteprednol etabonate is preferably formulated as suspension in water, with further ingredients such as preservatives, stabilizers,

tonicity agents, thickeners, suspension stabilizers, excipients to adjust the pH, buffer systems and wetting agents. For further details of suitable excipients, reference is made for example to DE 19 947 234.

The pharmaceutical preparations of the invention may, besides the glucocorticoid for example loteprednol etabonate and the phosphodiesterase-4 inhibitor, for example N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide, active ingredients, comprise further ingredients such as customary preservatives, stabilizers, thickeners, flavorings, etc.

In a preferred embodiment of the invention, the phosphodiesterase-4 inhibitor composition is in the form of a nasal spray or of a metered aerosol or of a metered dry powder for inhalation. The glucocorticoid composition is preferably likewise a topical preparation, and for the soft steroid loteprednol a formulation in the form of nasal spray, metered aerosol or metered dry powder for inhalation is again preferred.

The active ingredients can be administered from once to six times a day. The active ingredients are preferably administered once to twice a day, particularly preferably twice a day. The dose of the phosphodiesterase-4 inhibitor (for example, the hydroxyindole derivative N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide or roflumilast) is approximately from 0.1 to 20 mg per day per adult, preferably between 0.2 and 5 mg. The dose of the glucocorticoid in partiuclar loteprednol, can be in the region of the approved dosage, i.e. in the range from 0.1 to 1.6 mg per day, preferably between 0.2 and 0.8 mg per day. The actual

dose depends on the general condition of the patients (age, weight, etc.) and the severity of the disease.

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CLAIMS

1. A composition comprising a glucocorticoid and at least one phosphodiesterase-4 inhibitor in fixed or free combination.

2. The composition as claimed in claim 1, characterized in that the glucocorticoid and the phosphodiesterase-4 inhibitor are active ingredients which can be administered topically.

3. The composition as claimed in claim 1 or 2, characterized in that the phosphodiesterase-4 inhibitor is rolipram, piclamilast, roflumilast, cilomilast, the hydroxyindole derivative N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide or mixtures thereof.

4. The composition as claimed in any of claims 1 to 3, characterized in that the glucocorticoid is a soft steroid.

5. The composition as claimed in any of claims 1 to 4, characterized in that the glucocorticoid is beclomethasone, budesonide, ciclesonide, fluticasone, mometasone or loteprednol or a pharmaceutically acceptable ester thereof.

6. The composition as claimed in claim 4 or 5, characterized in that the glucocorticoid is loteprednol etabonate.

7. A medicament for the treatment of respiratory diseases, allergic diseases, asthma and/or chronic obstructive pulmonary diseases, comprising as active ingredient a glucocorticoid and at least one phosphodiesterase-4 inhibitor in fixed or free

combination, where appropriate together with customary excipients or carriers.

8. The medicament as claimed in claim 7, characterized in that it can be administered topically.

9. The medicament as claimed in claim 8, characterized in that it can be administered simultaneously, sequentially or separately from one another, intranasally or by inhalation.

10. The medicament as claimed in claim 8 or 9, characterized in that it is an inhalable liquid or solid preparation.

11. The medicament as claimed in claim 7, characterized in that the phosphodiesterase-4 inhibitor can be administered orally.

12. A process for producing a medicament for the treatment and prophylaxis of respiratory diseases, allergic diseases, asthma and/or chronic obstructive pulmonary diseases, comprising as active ingredients a glucocorticoid and at least one phosphodiesterase-4 inhibitor, characterized in that the glucocorticoid and the phosphodiesterase-4 inhibitor(s) are mixed singly or together, where appropriate together with customary excipients and carriers, and the mixture obtained in this way is converted into suitable dosage forms.

13. The use of the fixed or free combination of a glucocorticoid and of a phosphodiesterase-4 inhibitor for producing a medicament for the treatment and prophylaxis of respiratory diseases, allergic diseases, asthma and/or chronic obstructive pulmonary diseases.

14. The use as claimed in claim 13, characterized in

that the glucocorticoid is loteprednol etabonate and the phosphodiesterase-4 inhibitor is the hydroxyindole derivative N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide.

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Abstract

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